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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,782	07/09/2001	Susan Hardin	IVGN 1013	9388
7590 Todd R. Walters, Esq. BUCHANAN INGERSOLL & ROONEY PC 1737 King Street, Suite 500 Alexandria, VA 22314			EXAMINER SISSON, BRADLEY L	
			ART UNIT	PAPER NUMBER
			1634	
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			05/28/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/901,782

Applicant(s)

HARDIN ET AL.

Examiner

Bradley L. Sisson

Art Unit

1634

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) See Continuation Sheet is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 March 2006 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF-08)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

Continuation of Disposition of Claims: Claims pending in the application are 10,16-18,50,51,53-55,64,65,67-69,71,72,74,76,77,79-82,84-87,89-92,95-98,100,102-106 and 108-111.

Continuation of Disposition of Claims: Claims rejected are 10,16-18,50,51,53-55,64,65,67-69,71,72,74,76,77,79-82,84-87,89-92,95-98,100,102-106 and 108-111.

DETAILED ACTION

1. The following is a supplemental Office action. The period of response is reset to run from the mail date of the instant action.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 14 December 2009 has been entered.

Specification

3. The specification remains objected to as documents have been improperly incorporated by reference. It is noted that the specification contains reference to numerous documents, yet the complete bibliographical citation has not been provided. In general, only the last name of the first named author and publication year are provided. A review of the original specification fails to find where any bibliographical index has been provided. As a consequence, it is not readily apparent as to just which journal(s) the publications appeared in, much less identify where in the various articles the essential materials is to be found. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. See *General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** See *In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application). (Emphasis added.)

4. Accordingly, the cited documents are not considered to have been incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.
5. The disclosure is objected to because of the following informalities:
 - a. At page 31 of the disclosure appears the "DESCRIPTION OF THE DRAWINGS," which comprises a description of Figures 1, 2, 3A-C, 4, 5, and 6. The application, however, was filed with Figures 1-12. The specification needs to be amended so to provide a brief description of Figures 7-12.
 - b. At pages 55 and 56 appear graphic inserts/cells of chemical formulae and reactions. The lettering of the graphics is objected to for not being of sufficient size so as

to lend itself to effective reproduction. Applicant is urged to consider moving these illustrations into new Figures. If such a strategy is adopted, applicant is reminded to also include a brief description of any new figure added.

6. Appropriate correction is required.

Drawings

7. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because:

- a. The lettering is not of proper size, uniform density, and well-defined in Figure(s) 2, 3A, 3B, 4-7, and 9-11. See 37 CFR 1.84 (l) and (p)(1) – (5). (“Numbers, letters, and reference characters must measure at least .32 cm (1/8 inch) in height.”)
- b. The lines are not clean, well-defined, and of uniform thickness in Figure(s) 4. See 37 CFR 1.84(l) and (q).
- c. Replacement sheets are not properly identified in FIG(s) 1-12. See 37 CFR 1.84(c).
- d. The images/photographs are not of sufficient quality so that all details in the photographs are reproducible in printed patent- FIG(s) 8, 10, and 11 . See 37 CFR 1.84(b)(1).

8. Applicant is advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, are required by the examiner. The annotated drawing sheet(s) must be clearly labeled as "Annotated Sheet" and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35

U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,982,146 B1 (Schneider et al.) in view of US Patent 7,037,687 B2 (Williams et al.) and US Patent 6,306,607 B2 (Williams).

13. It is noted that while Schneider et al., was published 03 January 2006, it claims benefit of priority to provisional application 60/151,580, filed 30 August 1999. In comparison, the instant application claims benefit of priority to provisional application filed 07 July 2000. Accordingly, Schneider et al., qualifies as 102(e)-type art.

14. Attention is directed to the decision in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007):

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

15. It is further noted that prior art is not limited to the four corners of the documentary prior art being applied. Prior art includes both the specialized understanding of one of ordinary skill in the art, and the common understanding of the layman. It includes “background knowledge possessed by a person having ordinary skill in the art. . . [A] court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR* at 1396.

16. Suggestion, teaching or motivation does not have to be explicit and “may be found in any number of sources, including common knowledge, the prior art as a whole or the nature of the problem itself” *Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007) citing *Dystar Textilfarben GMBH v. C. H. Patrick Co.*, 464 F.3d 1356 (Fed. Cir. 2006).

17. Schneider et al., disclose methods, and related compositions, for conducting sequencing reactions. As seen at column 5, the polymerase and nucleotides are both labeled, and that can serve as either a donor or acceptor of a signal, which can be fluorophores.

18. Schneider et al., column 9, teach explicitly of the application of fluorescence resonance energy transfer (FRET). Schneider et al., column 10, teaches, “[o]ne of ordinary skill in the art can easily determine...which fluorophores will make suitable donor-acceptor FRET pairs. Such a showing meets a limitation of claims 18, 55, 69, 77, 87, and 98.

19. Schneider et al., column 13, disclose a plethora of polymerizing agents, which include DNA polymerase I, Taq polymerase, reverse transcriptase, and RNA polymerase.
20. Schneider et al., column 25, teach that the fluorophore can be linked directly or indirectly to the nucleotide.
21. Schneider et al., column 9, teach that the donor and acceptor fluorophores need to be within 10 to 100 Angstroms of one another for fluorescence resonance energy transfer to take place. Such a showing is considered to meet the limitation of 10, 15, or 25 Angstroms-limitations of claims 80, 81, 105, 106
22. Schneider et al., column 24, first full paragraph, teach that the linkage which couples the fluorophore to the nucleotide can be designed such tat it is cleaved, thereby releasing the fluorophore, prior to the incorporation of the next nucleotide.
23. While Schneider et al. disclose numerous polymerases, they do not teach specifically if the polymerases lack exonuclease activity. Additionally, Schneider et al., do not teach that the fluorescent label is released from the nucleotide by action of the polymerase (i.e., cleavage of the terminal phosphates).
24. Williams et al., column 4, teach that their method utilizes polymerases that are deficient in exonuclease activity.
25. Williams et al., column 7, disclose polymerases that are useful in such a procedure. As seen therein, one such polymerizing agent is *Taq* polymerase as well as T7 DNA polymerase, Klenow polymerase, reverse transcriptase, etc.
26. Williams et al., column 12, bridging to column 13, disclose using fluorescently-labeled nucleotides, and their being incorporated by the aforementioned polymerases.

27. Williams et al., column 7, disclose compositions which are used to carry out various reactions. Said compositions are described as comprising the above identified nucleotides and polymerases.
28. Neither Schneider et al., nor Williams et al., have been found to disclose using nucleotide where the fluorescent label is attached to a terminal phosphate.
29. Williams discloses methods and related kits for detecting incorporation of a nucleotide by a polymerase where the nucleotide comprises a label attached to the terminal phosphate, and that the terminal phosphate is cleaved by action of the polymerase, thereby releasing a member of a FRET pair into solution.
30. Williams, column 2, states:

Fluorophore-quencher pairs have been incorporated into oligonucleotide probes in order to monitor biological events based on the fluorophore and quencher being separated or brought within a minimum quenching distance of each other. For example, probes have been developed wherein the intensity of the fluorescence increases due to the separation of the fluorophore-quencher pair. Probes have also been developed which lose their fluorescence because the quencher is brought into proximity with the fluorophore. These fluorophore-quencher pairs have been used to monitor hybridization assays and nucleic acid amplification reactions, especially polymerase chain reactions (PCR), by monitoring either the appearance or disappearance of the fluorescence signal generated by the fluorophore molecule. (Emphasis added)

Nucleotide triphosphates having a fluorophore moiety attached to the .gamma.-phosphate are of interest as this modification still allows the modified NTPs to be enzyme substrates. For instance, Felicia et al., describe the synthesis and spectral properties of a "always-on" fluorescent ATP analog, adenosine-5'-triphospho-.gamma.-1-(5-sulfonic acid)-naphthyl ethylamindate (.gamma.-1,5-EDANS)ATP. The analog is a good substrate for E. Coli RNA polymerase and can be used to initiate the RNA chain. The ATP analog is incorporated into the RNA synthesized and is a good probe for studies of nucleotide-protein interactions, active site mapping and other ATP-utilizing biological systems (see, Felicia et al., *Arch. Biochem Biophys.*, 246: 564-571 (1986)).

31. Williams also teaches that nucleotides can comprise both quencher and donor fluorophores. While a nucleotide comprising both donor and quencher may not function with the system of Schneider et al., one of ordinary skill in the art would have been motivated to have adopted the aspect disclosed by Williams of where a nucleotide comprises one member of a FRET pair on the terminal phosphate and the other member of the FRET pair on the polymerase. As Williams clearly set out, in order for a FRET pair to be functional, they must be in close proximity to one another. If you are to detect a change in FRET as a result of incorporation, one must disrupt the FRET pair. To do so, there are but two options- either you have both members on a nucleotide, where one is cleaved, or you have one on the polymerase (Schneider et al.) and one on the terminal phosphate of the nucleotide (Williams). Said ordinary artisan would have been motivated to have one member of the FRET pair on the terminal phosphate versus at some other position of the nucleotide, as the polymerase would cleave the terminal phosphates, therein removing the label and eliminating the signal associated therewith. If, in the alternative, the FRET member had been retained on the nucleotide subsequent to incorporation, it would be expected to produce a signal until such time that it had been moved the requisite distance from its corresponding FRET member as a result of additional nucleotide incorporations by the polymerase- which is estimated to be about 20 nucleotides. The direct consequence of having retained both members of the FRET pair would be an inability for the artisan to effectively determine just which nucleotide(s) had been incorporated by the polymerase. Given the predictable nature of the fluorescent moieties, the obvious advantages readily apparent to one of skill in the art, and the limited number of possible combinations, it would have been obvious to one of ordinary skill in the art to have modified the nucleotides of Schneider et al., and Williams

et al., whereby one member of a FRET pair was attached to the terminal phosphates of a nucleotide and the other FRET pair member being attached to the polymerase (Schneider et al., and Williams et al.)

32. For the above reasons, and in the absence of convincing evidence to the contrary, claims 10, 16-19, 50-56, 64-74, 76-92, 94-100, 102-106, and 108-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,982,146 B1 (Schneider et al.) in view of US Patent 6,306,607 B2 (Williams) and US Patent 7,037,687 B2 (Williams et al.).

Conclusion

33. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

34. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

36. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

37. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/
Primary Examiner, Art Unit 1634